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THE STRUCTURE OF FERRUDIOL, A HIGHLY OXIDIZED CONSTITUENT OF *UVARIA FERRUGINEA*[1]

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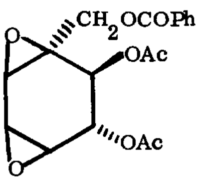
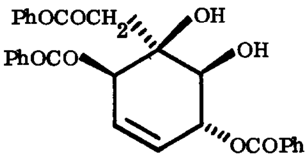
Summary: Using spectroscopic and chemical methods, the title compound has been shown to possess stereostructure 1 or its mirror image.

In recent years, plants of the genus *Uvaria* have provided a fascinating array of secondary metabolites possessing polyoxygenated cyclohexane skeletons.[3-5] Crotepoxide[6] and senepoxide[7] are two biologically active members of this unusual group. As part of an ongoing program to elucidate the chemical constituents from Asian species in this genus,[8] we now report the structure elucidation of ferrudiol 1, isolated from *Uvaria ferruginea.*



crotepoxide



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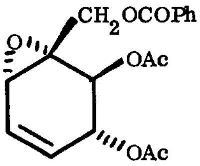


senepoxide

A sample of the plant, morphologically similar to *U. purpurea,* was collected near Khonkhaen University in northeast Thailand. The air-dried mass (10 kg) was ground, then extracted with n-hexane for 2 weeks at room temperature. Concentration of the crude extract caused precipitation of vegetable matter. Filtration followed by further concentration yielded a dark residue. Silica gel column chromatography (EtOAc/hexane, 30 :70) gave a colorless solid which upon recrystallization afforded 105 mg of pure ferrudiol 1 [mp 191-192°C($CHCl_3$/hexane); $[\alpha]_D^{20}$-141° (c 0.91, $CHCl_3$)].

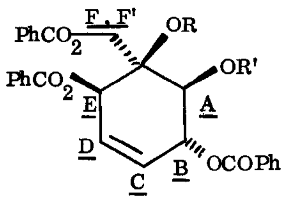
The molecular formula $C_{28}H_{24}O_8$ was derived from CIMS [methane, m/z 489(M+H$^+$, 0.2%)] and confirmed by combustion analysis [%C calc. 68.85, found 68.65; %H calc. 4.92, found 4.92; %O calc. 26.23, found 26.43]. Examination of all the spectral data indicated the presence of three benzoate moieties [m/z 367(M+H$^+$ - $PhCO_2H$, 13.5%), 245(M+H$^+$ - 2 $PhCO_2H$, 11.4%), and 123 (M+H$^+$ -3 $PhCO_2H$, base); NMR δ 7.16-8.25 (15H); IR(KBr) 5.90 μ; UV λ_{max}^{MeOH} = 230 nm(ε 54,545), λ=267 nm(ε 3,370), 273 nm(ε 3,700) and 281 nm(ε 3,370)], a cis disubstituted olefin [δ 5.80(1H, dd J=11,1 Hz) and 5.98(1H, dd J=11, 1.5 Hz); IR 14.2 μ] and at least one hydroxyl group [m/z 471(M+H$^+$ -H_2O, 0.6%); IR 2.95 μ] in ferrudiol. These functionalities contribute $C_{23}H_{18}O_7$ towards the molecular formula and account for 16 of 17 degrees of unsaturation inherent in the formula.

The 300 MHz ^{1}H NMR spectrum of ferrudiol revealed at least seven C-H resonances (see Table) upfield from the aromatic region, many of which closely resembled features of the pipoxide spectrum.[8] Addition of D_2O to the sample caused sharpening of a one-proton doublet at δ 4.32 (J=9 Hz) due to a secondary hydroxyl group. Exhaustive benzoylation of ferrudiol produced both tetrabenzoate 2 [mp 171-73°C; m/z 593(M+H$^+$, 1.2%); δ 7.16-8.3 (20H, complex)], and pentabenzoate 3 [δ 7.16-8.3 (25H, complex)], thus confirming two hydroxyl functions in ferrudiol. With benzoyl chloride/triethylamine, 1 slowly formed tetrabenzoate 2, whereafter addition of N, N-dimethylaminopyridine to the reaction and raising the temperature to 50-60°C promoted pentabenzoate formation, suggesting that the second hydroxyl group was tertiary. Similar behavior was observed upon acetylation, leading to 4 and 5.

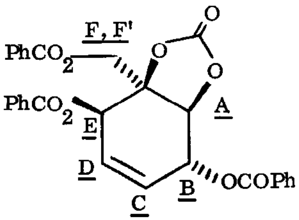
Extensive proton decoupling experiments on the well-resolved pentabenzoate 3 unambiguously supported its ene-dibenzoate substructure as well as the presence of a distinct AB spin system linked to the ring's quaternary center. Heating ferrudiol in toluene with N,N'-carbonyldiimidazole furnished cyclic carbonate 6 [mp 80-83°C; CIMS (methane) m/z 515(M+H$^+$, 1.3%)] in which one proton signal (H_A) was shifted sharply downfield, thus demonstrating a cis-vicinal relationship between the secondary and tertiary hydroxyl groups in 1. Moreover the observed J value of 9.5 Hz for H_A, by analogy to other related cyclohexanes,[8] was consistent with a trans-diaxial coupling to H_B. Having secured the constitution of 1 around C7-C1-C2-C3, attention was turned to the relative stereochemistry of ferrudiol's C3 and C6 benzoate substituents.

Catalytic hydrogenation of 1 (H_2/Pd-C/Et_2O/rt/6h) gave dihydroferrudiol 7 [mp 83-84°C; NMR (see Table); CIMS (methane) m/z 491(M+H$^+$, 3%), 473(M+H$^+$ -H_2O, 15%), 369(M+H$^+$-$PhCO_2H$, 47%), and 105 ($PhC{\equiv}O^+$, base)]. Besides shifting the two allylic methine proton signals H_B and H_E to higher field, saturation of the double bond created two readily distinguishable ABX spin systems ($H_BH_CH_{C'}$, $H_EH_DH_{D'}$). Coupling constants for J_{BC}(9.5 Hz) and $J_{BC'}$(4.8 Hz) confirmed the equatorial disposition already assigned to the C3 benzoate. It followed similarly that the axial-

TABLE



1 R,R' = H
2 R = H, R' = COPh
3 R,R' = COPh
4 R = H, R' = Ac
5 R,R' = Ac



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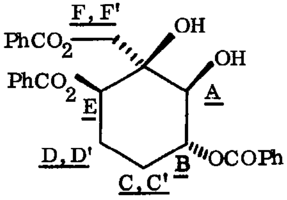

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NMR DATA (δ, $CDCl_3$, 300 MHz)

	H_A	H_B	H_C	$H_{C'}$	H_D	$H_{D'}$	H_E	H_F, $H_{F'}$
1	4.32 (d, 9.5Hz)	5.83 (dd, 9.5, 1Hz)	5.80 (dd, 11, 1Hz)		5.98 (dd, 11, 1.5Hz)		5.85 (d, 1Hz)	4.75, 4.81 (AB quartet, 11Hz)
2	6.05 (d, 8Hz)	6.15 (dddd, 8, 2.5, 2, 2Hz)	6.06 (ddd, 11, 2.5, 2Hz)		6.18 (ddd, 11, 2.5, 2Hz)		6.08 (ddd, all 2.5Hz)	4.87, 4.95 (AB quartet, 13.5Hz)
3	6.96 (d, 5Hz)	6.03 (dddd, 5, 3.5, 1, 1Hz)	6.32 (ddd, 12, 3.5, 1Hz)		6.37 (ddd, 12, 3.5, 1Hz)		6.72 (ddd, 3.5, 1, 1Hz)	5.16, 5.55 (AB quartet, 15Hz)
4 (Ac δ1.93)	5.75 (d, 9Hz)	5.93 (d, 9Hz)	5.92 (d, 10.5Hz		6.07 (dd, 10.5, 1.5Hz)		5.94 (br. s)	4.78 (s)
5 (Ac δ2.02 2.05)	6.58 (d, 8Hz)	5.93 (dddd, 8, 3.5, 2.5, 2.5)	5.97 (ddd, 12, 3.5, 2.5Hz)		6.07 (ddd, 12, 2.5, 2.5Hz)		6.85 (ddd, all 2.5Hz)	4.78, 5.07 (AB quartet, 13.5Hz)
6	4.88 (d, 9.5Hz)	6.18 (dddd, 9.5, 2.5, 1.5, 1)	5.98 (ddd, 10.5, 2, 1.5Hz)		6.12 (ddd, 10.5, 2.5, 1.5Hz)		6.28 (ddd, 2, 1.5, 1Hz)	4.89, 4.99 (AB quartet, 13Hz)
7	4.02 (d, 9.5Hz)	5.39 (ddd, 9.5, 9.5, 4.8Hz)	2.36 (dddd, 13.5, 4.8, 4.5, 4.5Hz)	1.78 (dddd, 13.5, 9.5, 9.5 4.5Hz)	2.24 (dddd, 13.8, 4.5, 4.5 4.5Hz)	2.02 (dddd, 13.8, 10.3, 9.5 4.5Hz)	5.27 (dd, 10.3, 4.5Hz)	4.82, 4.88 (AB quartet, 12Hz)

axial(10.3 Hz) and axial-equatorial(4.5 Hz) couplings of H_E to its neighbors were only compatible with an equatorial C6 benzoate group. Thus ferrudiol possesses overall stereostructure 1 with all four bulky substituents equatorial around the cyclohexene half-chair.

The absence of an epoxide ring in ferrudiol distinguishes this structure from other highly oxidized, naturally -occurring cyclohexanes. While there are superficial similarities between 1 and seneol,[7] the all-*cis* arrangement of oxygens spanning the C6-C1-C2 portion of ferrudiol would represent the unusual *cis*-hydrolysis of a precursor oxirane. Synthetic studies designed to interrelate these structures and their absolute configurations are underway.

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